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Studies on Surgical Adjuvant Chemotherapy for Cancer of the Esophagus — Especially the Administration of Bleomycin into the Lumen of the Esophagus using Double Balloon Catheter and Iontophoresis

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Introduction

Recently, the result of the treatment of esophageal cancer has improved gradually, but the curability of this cancer is much more difficult than that of other cancers of the gastrointestinal tract¹⁾³⁷⁾. Most causes of death are metastases towards the lymph nodes and other organs³¹⁾³³⁾³⁴⁾³⁸⁾⁴³⁾. The rate of 5-year survival has been relatively improved by the adjuvant radiation therapy and chemotherapy¹⁾²⁾⁴⁾⁸⁾¹⁹⁾²⁸⁾. For the purpose of improving this rate, the author studied the local adjuvant chemotherapy, especially the administration of Bleomycin (BLM) into the lumen of the esophagus and local injection of BLM into the esophageal wall.

Chapter 1. Fundamental investigations on the local adjuvant chemotherapy.

Among local chemotherapies for cancer of the esophagus, the administration of BLM into the lumen of the esophagus and the intramural injection of BLM were investigated. In these experiments, the concentrations of BLM in various body fluids and organs were determined by bioassay, the Band Culture Method (by ÔKUBO, in 1955)³²⁾. The strain of test organism : bacillus subtilis PCI 219. Number of organisms : 2.1×10^7 /ml. Medium : Müller-Hinton medium. Incubation time (37°C) : 5-7 hours. Minimum inhibition concentration : 0.25mcg/ml⁴⁰⁾.

Blood and lymph were centrifuged at 2000 rpm for 5 minutes, and their supernatant fluids were used for the measurement. In order to determine BLM concentration in the organs, the animals were sacrificed by exsanguination and their resected tissues were homogenized

Key words : Bleomycin, Adjuvant chemotherapy, BLM-Iontophoresis, Double balloon catheter, Esophageal cancer

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into an emulsion and diluted with the physiological saline solution twice the volume as that of the homogenate. These homogenates were kept in a refrigerator at 4°C for 24 hours. These supernatant fluids were used for the measurement of BLM concentration.

(1) *Distribution of BLM following intramural injection of BLM solution.*

Materials and methods: Adult mongrel dogs weighing about 7kg were anesthetized by intramuscular injection of ketamine chloride at a dose of 10mg/kg and the respiration was controlled by intratracheal intubation with a respirator. In the dog, thoracotomy was carried out through the 6th intercostal space and a "cutdown" tube was inserted from the external jugular vein into the azygos vein via the superior caval vein to collect the azygos vein blood. The femoral vein was also cannulated by a "cutdown" tube to collect the femoral vein blood. Thereafter, in the left supraclavicular region of the dog the thoracic duct was separated and cannulated with a 21 G elastic needle to collect the thoracic duct lymph samples. The dog was injected with a BLM solution at a dose of 2 mg/kg into the submucosal layer of the middle thoracic esophagus. BLM concentration in the femoral vein blood, azygos vein blood and thoracic duct lymph were measured during 2 hours following injection.

Results : When BLM solution was injected into the middle thoracic esophagus, the drug was detected in the azygos vein blood five minutes after injection and arrived at a peak level 15 minutes after injection. Thereafter, the concentration decreased gradually. In the femoral vein blood, BLM levels were detected 5 minutes later and arrived at a peak level 30 minutes after injection, and in the thoracic duct lymph it reached the peak 15 minutes after injection (Fig. 1). BLM levels in each portion of the esophagus 30 minutes after the submucosal injections showed the highest values in the injected portion (Im) and decreased gradually in the portions oral and aboral to the injected portion. But 120 minutes after the injection, BLM remained only in a slight amount in the injected portion of the esophagus, because it was being absorbed into blood and lymph (Fig. 2). BLM concentration in the regional lymph nodes 30 minutes after the injection is shown in Fig. 3. It showed the highest level in the upper thoracic paraesophageal lymph nodes (105) and decreased gradually in the paratracheal lymph nodes (106), bifurcation lymph nodes (107) and pulmonary hiatus lymph nodes (109), in the order mentioned. BLM was detected only in a slight amount in the cervical and abdominal lymph nodes (Fig. 3). Among BLM levels of the other organs, it showed higher levels in the kidneys and the lungs. That is to say, on the injection of BLM solution into the submucosal layer of the esophagus, the drug spread itself toward the oral and aboral portions of the esophagus, by way of intramural lymphatics, reaching regional lymph nodes in great amounts, and was absorbed into the blood flow for a short period, then distributed in the lungs and the kidneys.

(2) *Administration of BLM into the lumen of the esophagus.*

In 1973, NISHIMURA noticed the effect of intraluminal administration of BLM on unresectable esophageal cancer³⁰⁾. SHIBATA performed some fundamental studies on this method of administration⁴⁰⁾. The author invented a specially designed double balloon catheter for the

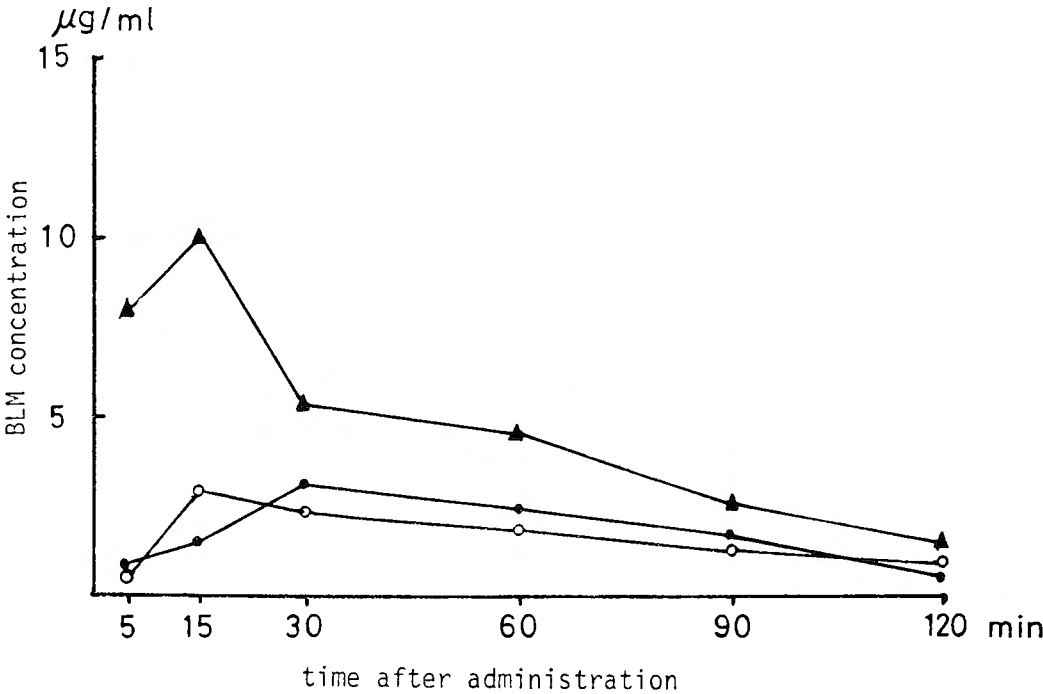


Fig. 1. BLM levels of blood and lymph following intramural injection of 2 mg/kg of BLM into the middle thoracic esophagus of dogs. \blacktriangle — \blacktriangle azygos vein, \bullet — \bullet femoral vein, \circ — \circ thoracic duct lymph.

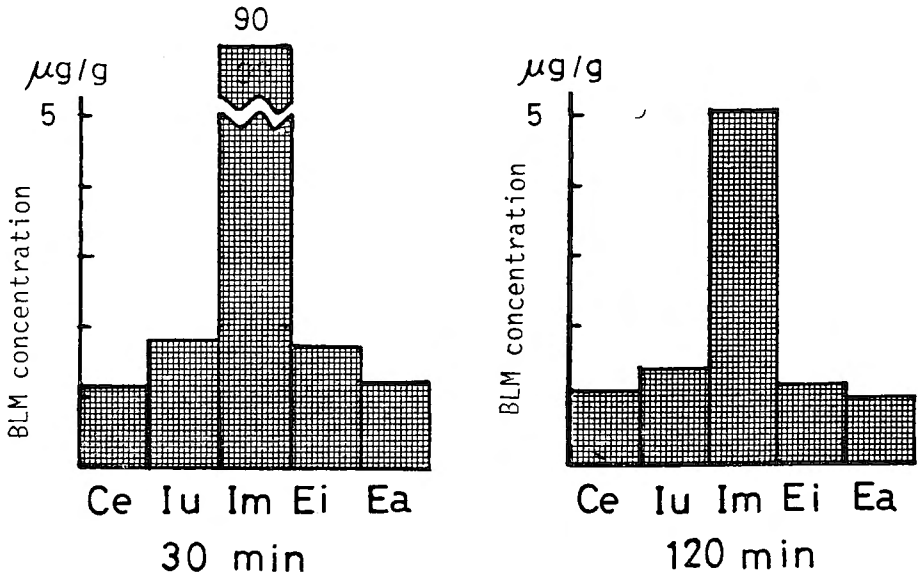


Fig. 2. BLM levels in each portion of the esophagus 30 min and 120 min after the intramural injection of 2 mg/kg of BLM into the middle thoracic esophagus of dogs.

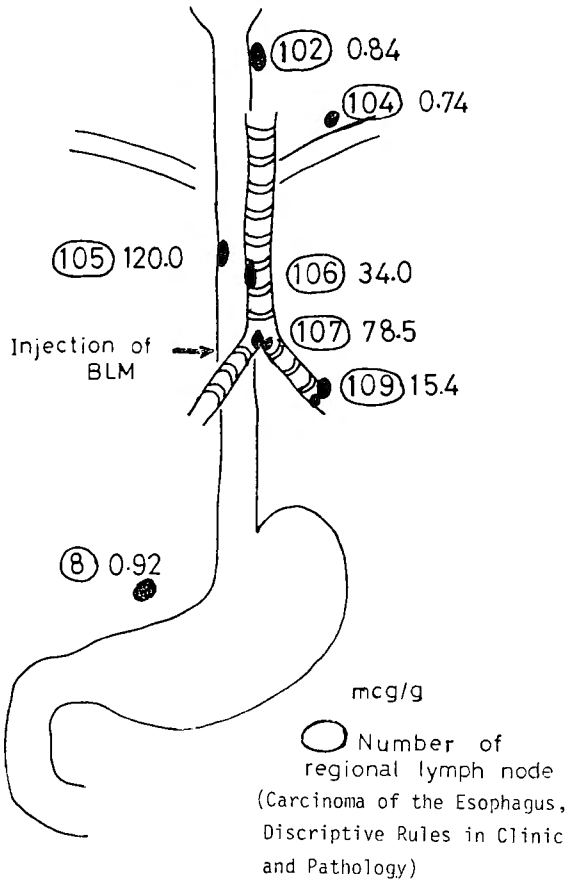


Fig. 3. BLM concentration in the regional lymph nodes 30 min after intramural injection of 2 mg/kg of BLM.

intraluminal administration of BLM. It consists of two balloons and two catheters. The distance between two balloons is 10cm (Fig. 4).

Materials and methods : Mongrel dogs, weighing about 7kg, were anesthetized with the above-mentioned method, and a double balloon catheter was inserted from the mouth into the lumen of the esophagus. In the cervical esophagus, double balloons were inflated by air, maintaining intraballoon pressure at 20mmHg. Thereafter, the physiological saline solution of BLM, 2 mg/ml, was infused into the lumen of the esophagus, which was obstructed by two inflated balloons, at a dose of 2 mg/kg, and detained for 2 hours. BLM levels in the azygos and femoral vein bloods and the thoracic duct lymph were measured for 2 hours following infusion. After 2 hours, the dogs were sacrificed by exsanguination and BLM concentrations in each portion of the esophagus and in the other organs were measured by bioassay.

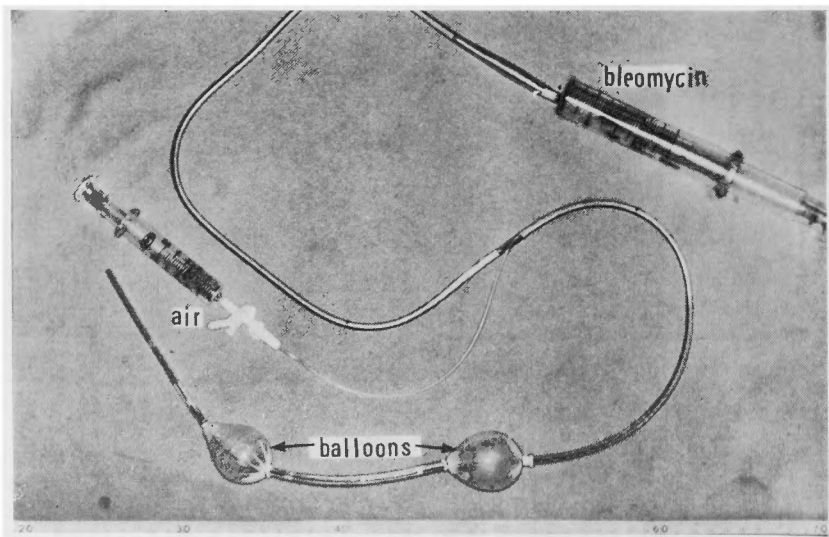


Fig. 4. Double balloon catheter

Moreover, in order to observe the absorption of BLM from the esophageal lumen, right thoracotomy was carried out through the 10th intercostal space and the lower thoracic esophagus was exposed in the dog. The mucosa of the esophagus was exposed by esophagotomy and resected annularly 4cm in length or in an elliptical shape, 4 cm in length and 2 cm in width. The wound of esophagotomy was closed completely by No. 4 silk sutures. The esophagus, whose mucosa was resected, was obstructed by double balloon catheter and was infused with BLM solution of the above-mentioned amount. In the dog, BLM levels of the azygos, femoral vein blood and the thoracic duct lymph were measured for 2 hours and BLM concentrations in various organs were measured 120 min. after infusion.

Results : On the intraluminal administration of BLM using a double balloon catheter, BLM could not be detected in blood and lymph in dogs when the mucosa of the esophagus was intact. However BLM was measured in a small amount in the cervical esophagus which had come in contact with BLM solution. BLM was not detected in the other organs. In the dogs with a complete annular defect of the esophageal mucosa, BLM levels in the azygos vein blood were detected 5 minutes after administration and arrived at a peak level 30 minutes after administration, and those in the thoracic duct and the femoral vein blood arrived at a peak level 90 minutes after administration and decreased gradually thereafter. In the dogs with an elliptical defect of the esophageal mucosa, BLM levels in the azygos vein blood were measurable 30 minutes after administration and arrived at a peak level after 60 minutes, and in the femoral vein blood and thoracic duct lymph arrived at a peak level 120 minutes after administration. Regarding BLM levels in various organs 120 minutes after administration, they were lower in the liver, spleen, kidneys and lungs than those after the injection of BLM into the esophageal wall, but BLM levels in the esophagus were higher after the intraluminal administration (Fig. 5).

That is to say, when BLM solution was administered into the lumen of the esophagus using a double balloon catheter, it was absorbed in slight amounts only through the normal esophageal mucosa, but BLM levels were sufficiently increased in absorption in proportion to the extent of the defect of the mucosa. The wider the mucosal defect was, the higher and the sooner the peak level of BLM in the blood and lymph appeared. Judging from changes in concentration of BLM in the blood and lymph, it is thought that the drug is absorbed from the lumen of the esophagus by way of both lymphatic and blood flows.

(3) *Fundamental experiments on BLM-Iontophoresis.*

As BLM is a glycopeptide ionized in cation, by the application of the direct current into BLM solution BLM molecules shifted to the cathode¹³⁾. BLM solution with the physiological saline showed an acidity of pH 5.2.

The author investigated the movement and inactivation of BLM and the permeance of BLM in the resected esophagus of the dog by the application of the direct current.

(i) Movement of BLM by the application of the direct current.

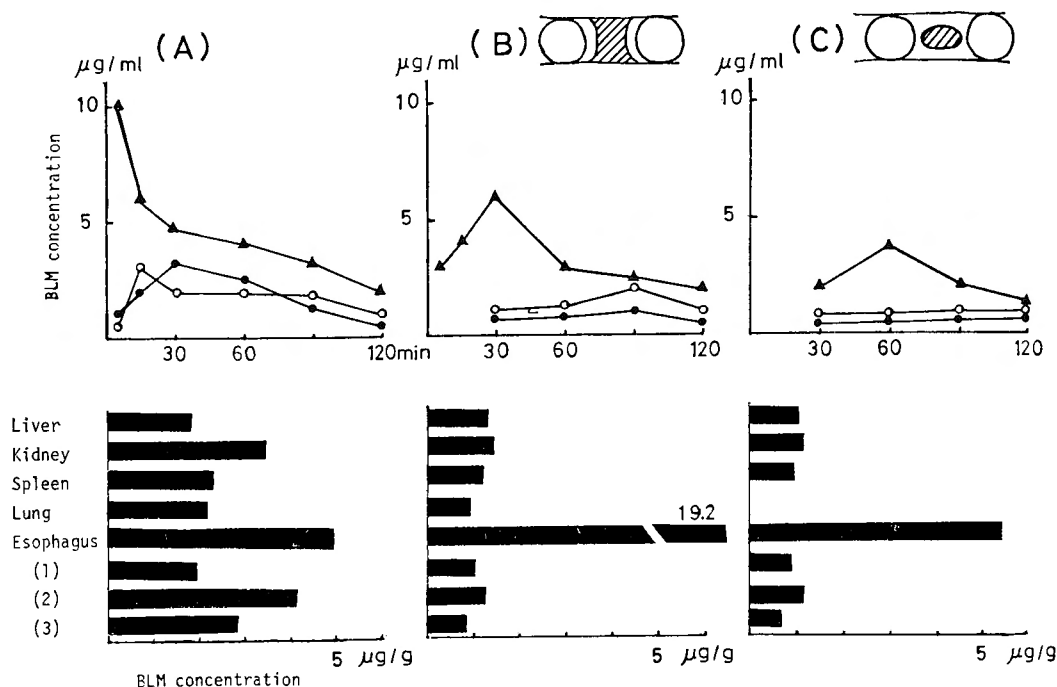


Fig. 5. Comparison of the distribution of BLM between intramural injection and intraluminal administration of BLM at the dose of 2 mg/kg. A) Intramural injection of BLM into the lower thoracic esophagus, B) Intraluminal administration of BLM into the lower thoracic esophagus with complete annular defect of the mucosa, 4 cm in length, C) Intraluminal administration of BLM into the lower thoracic esophagus with defect of the mucosa in an elliptical shape (4cm×2cm). ▲—▲ azygos vein, ●—● femoral vein, ○—○ thoracic duct lymph. (1) Cervical paraesophageal lymph nodes, (2) Thoracic paraesophageal lymph nodes, (3) Abdominal lymph nodes

Materials and methods : A small square hole, 4 mm×4 mm in size, was made in the 1 % agar gel plate, 7×6×0.6cm in size. The hole was filled with BLM solution. Thereafter, agar gel electrophoresis was performed under the condition of 10 mA for 30 minutes. The agar gel plate was cut into rectangles, 0.5×1.0cm in size, consecutively and BLM concentration in each piece of agar plate was measured.

Results : After electrophoresis of 10 mA for 30 minutes, the peak concentration of BLM in the agar culture plate shifted from 5 to 10 mm in the direction of the cathode and BLM was detected as far as 3 cm from the original site on the side of the cathode (Fig. 6).

(ii) BLM inactivation on iontophoresis.

Materials and methods : BLM inactivation on iontophoresis was investigated by means of BLM physiological saline solution after the application of the direct current of 5 mA, 10 mA and 20 mA for 30 minutes, respectively. Moreover, the inactivation of BLM in various solvents was investigated applying the direct current at 5 mA for 30 minutes. Five mg of BLM was dissolved with (1) physiological saline, pH 5.2, (2) $\frac{1}{10}$ N hydrochloric acid

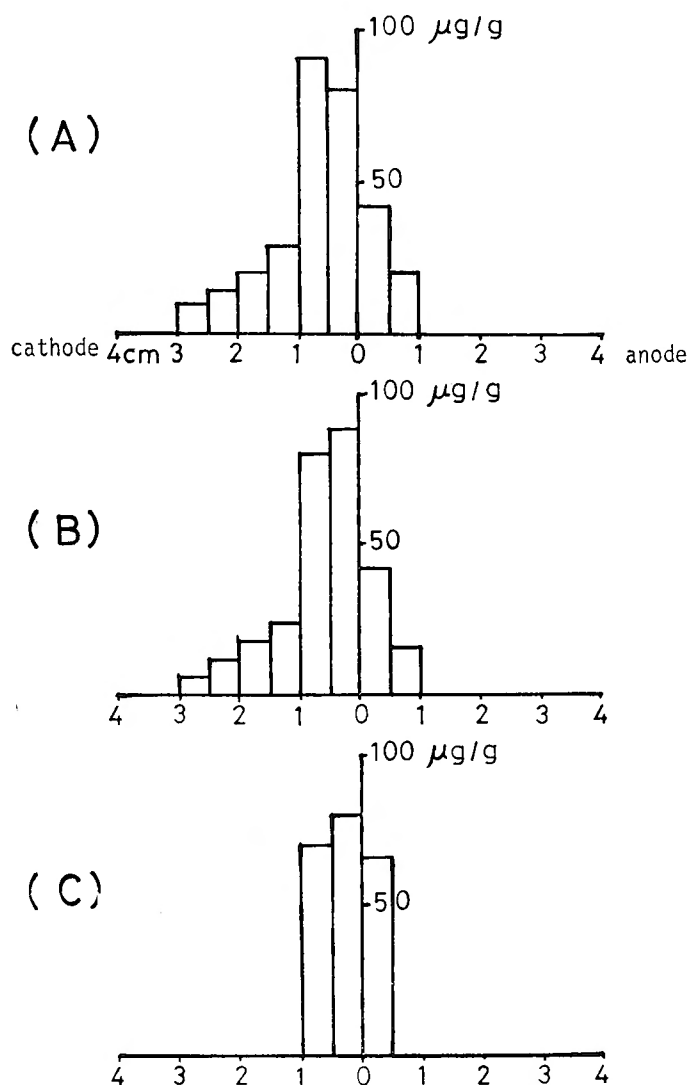


Fig. 6. Shift of BLM in 1% agar plate with various solvents caused by electrophoresis, 10 mA, for 30 min. A) 1% agar solved with physiological saline, pH 6.8, B) 1% agar solved with PBS, pH 7.2, C) 1% agar solved with $\frac{1}{16}$ N NaOH, pH 12.5.

solution, pH 2.3, (3) phosphate buffer solution, pH 7.6 and (4) $\frac{1}{16}$ N sodium hydroxide solution, pH 12.6.

Results : The inactivation of BLM by applying the direct current occurred approximately in proportion to the intensity of electric current and the duration of application (Fig. 7). The effects of electrization of 5 mA for 30 minutes was slight. When BLM was dissolved in various solvents and the direct current of 5 mA was applied for 30 minutes,

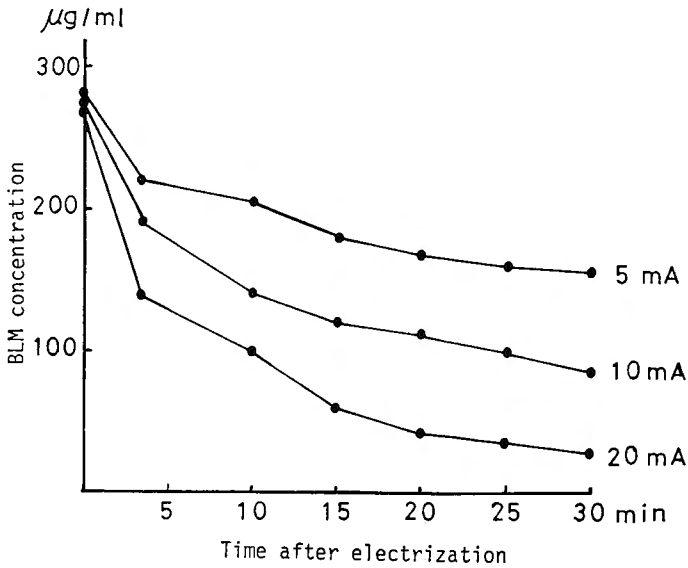


Fig. 7. Inactivation of BLM by electric current. Five mg of BLM were solved with 20 ml of physiological saline. Direct current applied at 5 mA, 10 mA and 20 mA for 30 min, respectively.

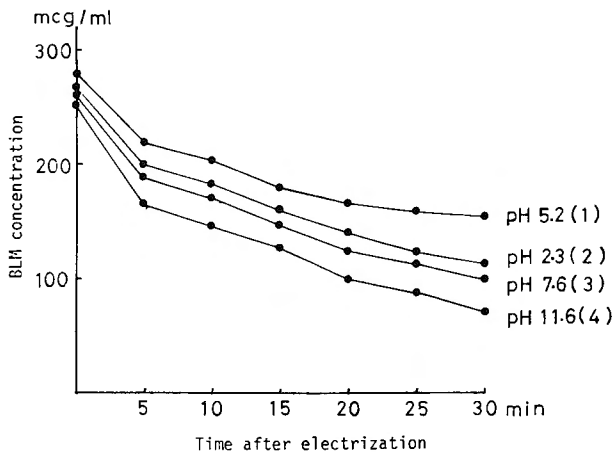


Fig. 8. Inactivation of BLM by electric current. Five mg of BLM were solved with 20 ml of various solvents. 1) physiological saline, pH 5.2, 2) $\frac{1}{10}$ N HCl, pH 2.3, 3) PBS, pH 7.6, 4) $\frac{1}{10}$ N NaOH, pH 12.6.

the inactivation occurred more intensely in the concentrated alkaline and concentrated acid solutions than in the physiological saline and phosphate buffer solutions (Fig. 8).

(iii) Permeance of BLM into the resected esophageal wall of the dogs.

Materials and methods : Permeance of BLM into the tissue was observed by means of two small vessels which were separated by the resected esophageal wall of the dog. The vessel on the mucosal side setting the anode was filled with 20ml of BLM solution in each

solvent containing 5 mg of the drug and the other vessel which was on the serosal side setting the cathode was filled with the same solvent. Direct current was electrized between both electrodes at the magnitude of 5 mA for 30 minutes. Thereafter, the resected esophageal wall was divided into the mucous and muscular layers and BLM concentration in each layer was measured. As solvents, (1) physiological saline, (2) phosphate buffer solution, (3) $\frac{1}{10}$ N hydrochloric acid solution and (4) $\frac{1}{10}$ N sodium hydroxide solution were used.

Results : When BLM was dissolved in such solutions as the physiological saline, phosphate buffer solution, $\frac{1}{10}$ N hydrochloric acid solutions, etc., the drug permeated well into the mucosal layer in great amounts and also into the muscular layer. But BLM was not detected in the muscular layer, when $\frac{1}{10}$ N sodium hydroxide solution was used as a solvent (Fig. 9).

(iv) Histological changes of the resected esophagus by the application of the direct current.

Materials and methods : As to the above-mentioned experiment of permeance of BLM,

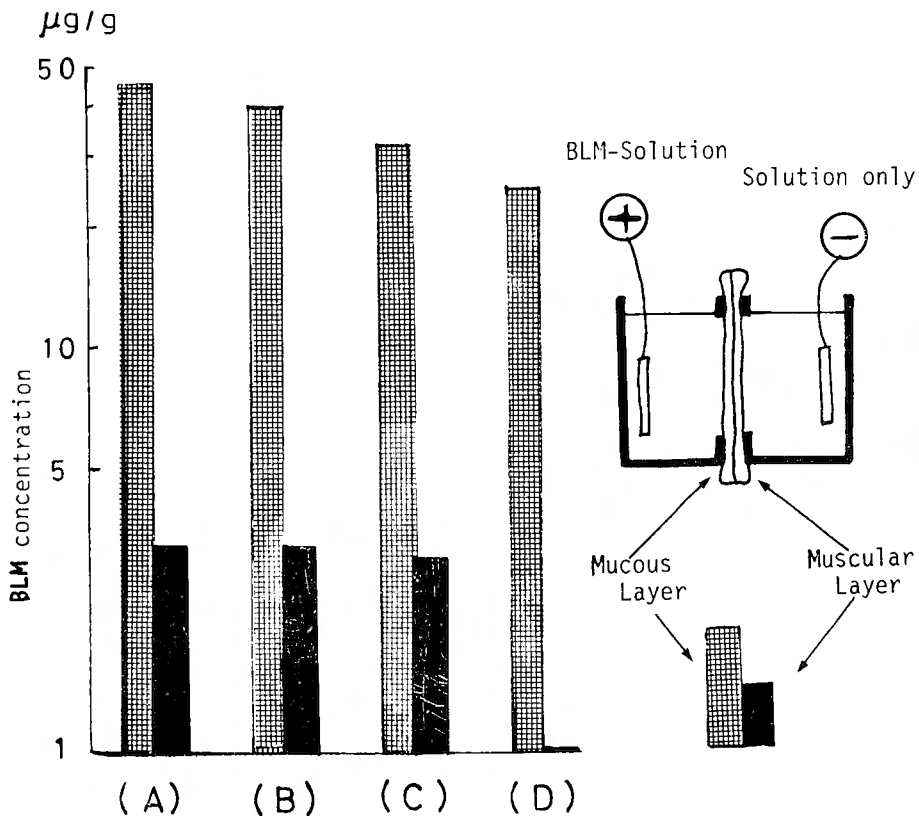


Fig. 9. Electrophoresis of BLM dissolved in various solvents into resected esophagus of dogs. Solvents : A) physiological saline, B) PBS, C) $\frac{1}{10}$ N HCl, D) $\frac{1}{10}$ N NaOH. Five mg of BLM was solved with 20 ml of the solvent. Direct current was applied at the 5 mA for 30 min.

the resected esophagi were electrized with the direct current at 20 mA, 10 mA, and 5 mA for 30 minutes, respectively, and these tissues were stained by hematoxylin-eosin and examined microscopically.

Results : When BLM-Iontophoresis was performed on the resected esophagus by electrization of 20 mA for 30 minutes, the tissue became thin and dehydrated. Microscopically, the epithelium showed a marked thinning, pyknosis and dehydration of the submucosal and muscular layers. On electrophoresis of 10 mA, the epithelium showed a slight thinning. At 5 mA, histological changes of the tissue were slight, except for a slight edema of the submucosal layer. Judging from the results of the above-mentioned fundamental experiments on BLM-Iontophoresis, the physiological saline may be an adequate solvent of BLM to the esophageal intraluminal administration of BLM using double balloon catheter combined with electrophoresis. This method can be performed with safety provided that the intensity of current is limited to less than 5 mA and the duration of the application does not exceed 30 minutes.

(4) *Administration of BLM into the lumen of the esophagus using double balloon catheter combined with iontophoresis.*

This experiment was performed presuming that when the intraluminal administration of BLM was used combined with iontophoresis, permeance of BLM into the wall of the esophagus and carcinoma tissues might be accelerated and the distribution of the drug to the regional lymph nodes might increase.

Materials and methods : Mongrel dogs weighing 8 to 10 kg were anesthetized with the above-mentioned method, and double balloon catheter, in which a silver electrode was set between both balloons, was inserted into the esophagus. The plate of copper was placed on the back of the dogs. BLM which was dissolved with the physiological saline was infused into the lumen of the esophagus between two inflated balloons at a dose of 2mg/kg. Direct current was electrized from silver electrode to the plate of copper at the magnitude of 5 mA for 30 minutes (Fig 10). Thereafter, BLM concentrations in each portion of the esophagus and lymph nodes were measured. BLM levels in the regional lymph nodes were determined in the cases when the balloon pressure was at 35 mmHg and 20mmHg, respectively. Moreover, in order to observe the route of permeance and the distribution of BLM, the dogs were administered with copper-containing BLM (copper content 3.42%) into the lumen of the esophagus between both balloons and electrophoresis was applied at 5 mA for 30 minutes. Then the dogs were sacrificed and the esophagi were resected. The copper ions in the esophagi were stained histochemically by the modified sulfide silver method by TIMM⁽⁴⁹⁾ (Table 1).

Results : When the intraluminal administration of BLM was used combined with iontophoresis, BLM level in the portion of the esophagus which was in contact with BLM solution was markedly high and moreover, the drug reached the regional lymph nodes (Fig. 11). In the concentration of the regional lymph nodes, the levels in thoracic lymph nodes were higher at 35 mmHg of balloon pressure than at 20 mmHg. But in remote

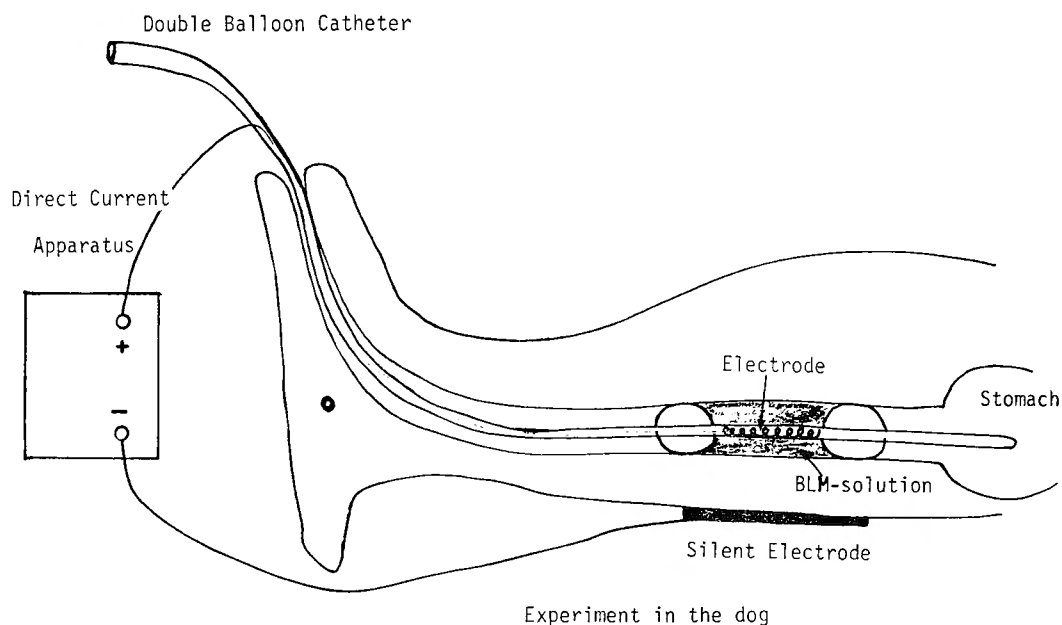


Fig. 10. Intraluminal administration of BLM using double balloon catheter combined with BLM-Iontophoresis.

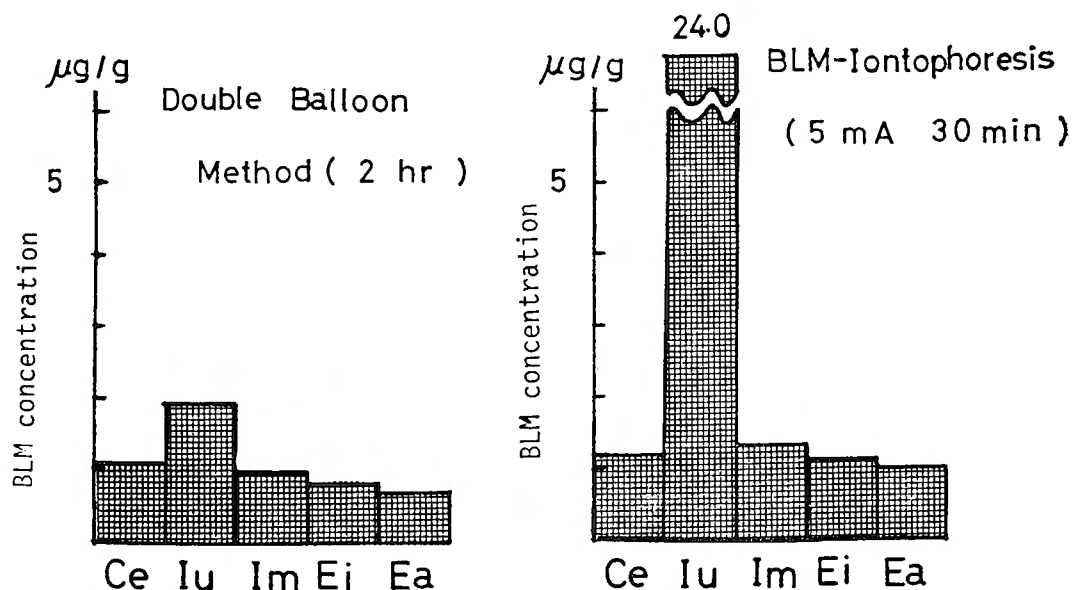


Fig. 11. Comparison of BLM concentration of each portion of the esophagus between intraluminal administration of BLM with BLM-Iontophoresis and that without BLM-Iontophoresis.

Table 1. Histochemical demonstration of copper-containing BLM.
(Silver sulfide method by Timm.)

- 1) Fresh resected tissue is fixed by dehydrated alcohol saturated with sulfured hydrogen sulfide.
 - 2) Fixed tissue is washed down excess hydrogen sulfide by dehydrated alcohol.
 - 3) Paraffine section is prepared.
 - 4) After removing the paraffine, the preparation is washed by distilled water.
 - 5) The preparation is stained with silvering by the following fluids between 30 and 60 min
 - A) fluid $\left\{ \begin{array}{l} 15\sim 20\% \text{ Gum arabic water solution : 10 ml} \\ 10\% \text{ Silver nitrate water solution } 0.2 \text{ ml} \end{array} \right.$
 - B) fluid $\left\{ \begin{array}{l} \text{Hydroquinone 2 g, Citric acid 3g} \\ \text{Distilled water 100 ml} \end{array} \right.$

All of A) fluid added 2ml of B) fluid is used for staining.
 - 6) Washing in distilled water.
 - 7) Staining with hematoxylin.
 - 8) Dehydration, transparency and enclosed by barsum.
- Results Copper is stained and becomes brownish colored granules.

lymph nodes, or cervical lymph nodes, BLM levels were higher at 20 mmHg of balloon pressure than those at 35 mmHg (Table 2). Microscopical observation was performed in order to clarify the distribution of copper-containing BLM. The copper, stained as black brownish granules, was scattered in the epithelium and tunica propria and filled the tracts of esophageal glands and its surrounding tissue (Fig 12). These findings show that BLM permeates into the esophageal wall through the normal mucosa from the lumen or via the tracts of esophageal glands in the opposite direction.

(5) Clinical evaluation of intraluminal administration of BLM for cancer of the esophagus.

Fourteen patients with esophageal cancer were treated with esophageal intraluminal administration of BLM using double balloon catheter. In 10 patients, it was used as pre-operative adjuvant chemotherapy. In three patients with unresectable cancer and one patient

with the recurrence of the esophageal cancer at the site of esophago-gastrostomy, this method was used as an ultimate treatment. Six patients who were treated with this method showed an improvement in swallowing and their appetites were improved after the performance of this method 3 or 4 times. Of the four patients who were unresectable cases, three cases showed a

Table 2. BLM concentration of regional lymph nodes under each balloon pressure. BLM was administered at a dose of 2 mg/kg into the lumen of the middle thoracic esophagus using double balloon catheter whose balloons were inflated under the pressure of 20 mmHg or 35 mmHg, combined with BLM-Iontophoresis (5 mA) for 60 min.

	Balloon Pressure 20 mmHg	Balloon Pressure 35 mmHg
Cervical Lymph Nodes	0.72 mcg/g	0
Thoracic Lymph Nodes	1.16	2.96
Abdominal Lymph Nodes	0.76	0.96



Fig. 12 Cu-BLM-Iontophoresis was performed at 5 mA for 30 minutes using double balloon catheter. The histology showed that black brownish granules of copper were scattered in the epithelium and filled the ducts of esophageal glands and its surrounding tissues. The stain was silver sulfide method by Timm. ($\times 100$)

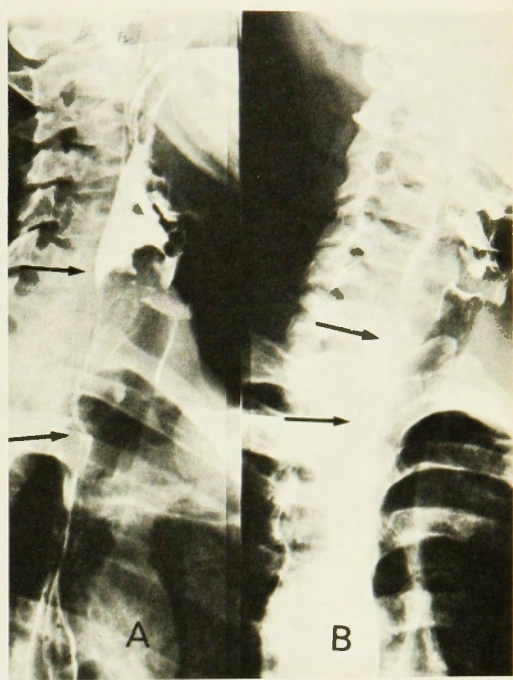


Fig. 13. Case 1. The esophagogram showed a long obstructing lesion in the cervical esophagus (A). After treatment of radiation and intraluminal administration of BLM, the cervical lesion improved markedly (B).

marked improvement by using radiation therapy at the same time.

Case 1 : A 50-year-old man with esophageal cancer (Ce)

On admission, he complained of a marked difficulty in swallowing and the double balloon catheter couldn't be inserted. On March 4, 1972, esophagogram revealed a markedly obstructing lesion in the cervical esophagus (Fig. 13, A). The histology was squamous cell carcinoma. He had metastatic tumors in both supraclavicular regions. In the first place, radiation therapy was given from March 10 to April 10, 1975. Thereafter, double balloon catheter could be inserted through the cervical lesion, and he was treated with esophageal intraluminal administration of BLM once a week as an outpatient. As a result of these treatments, esophageal and cervical metastatic lesions decreased in size markedly as seen in the esophagogram (Fig. 13, B), and the histology of the metastatic tumor showed a moderate effect of BLM (Ef-2) (Fig. 14).

Case 2 : A 42-year-old man with esophageal cancer.

One year ago he had undergone an operation for cancer of the esophagus, that was

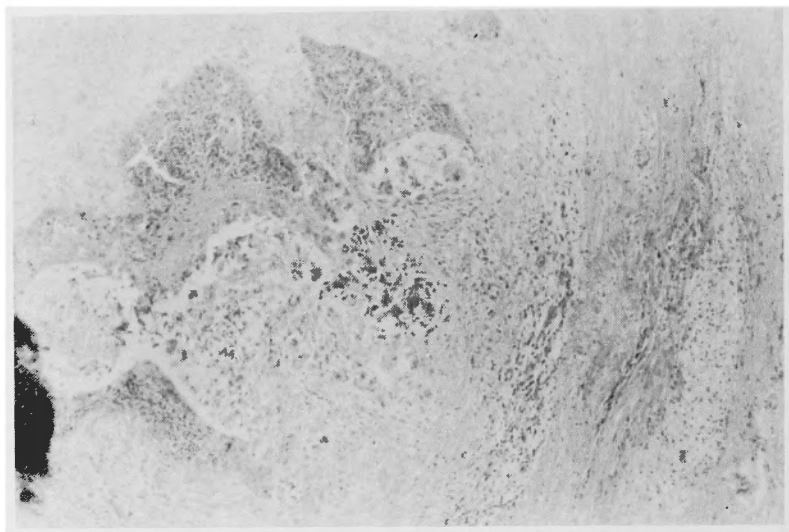


Fig. 14. Case 1. The histology was the left supraclavicular lymph node after treatment of intraluminal administration of BLM. Most of the cancer cells were degenerated and surrounded by connective tissue. Hematoxylin-eosin ($\times 100$)

subtotal esophagectomy and antethoracic esophagogastrostomy. The histology of the cancer was squamous cell carcinoma. One month ago, he had difficulty in swallowing and roentgenogram revealed an obstructing lesion at the site of the esophagogastrostomy in the left supraclavicular region in which a walnut-sized and hard tumor was palpated (Fig. 15.A). When he was treated with esophageal intraluminal administration of BLM using double balloon catheter combined with iontophoresis 3 or 4 times, he showed an improvement in swallowing as shown by the esophagogram (Fig. 15. B). Thereafter, radiation therapy was used at the same time. The tumor in the left supraclavicular region decreased in size markedly.

Case 3 : A 42-year-old man with esophageal cancer (Im, Ei).

Three months ago, he had suffered from difficulty in swallowing and consulted a doctor. On May 5, 1977, esophagogram revealed a long obstructing lesion, about 13 cm in length, in the lower two-thirds of the thoracic esophagus (Fig. 16, A). Endoscopy revealed an ulcerative type of the carcinoma. The histology was squamous cell carcinoma. He was treated with this method combined with iontophoresis 3 times. After the first performance, he felt a slight improvement in swallowing. After receiving this treatment 3 times, the esophagogram showed a slight improvement in swallowing and the ulcer was deepened (Fig. 16. B). A few days later, he had a slight spell of hematemesis. One week after this treatment, he received a radical operation for the esophageal cancer. The resected specimen of the esophagus showed an ulcerative type of carcinoma with necrotic tissue.

As in the above-mentioned cases, when the patient with cancer of the esophagus is treated with esophageal intraluminal administration of BLM using double balloon catheter

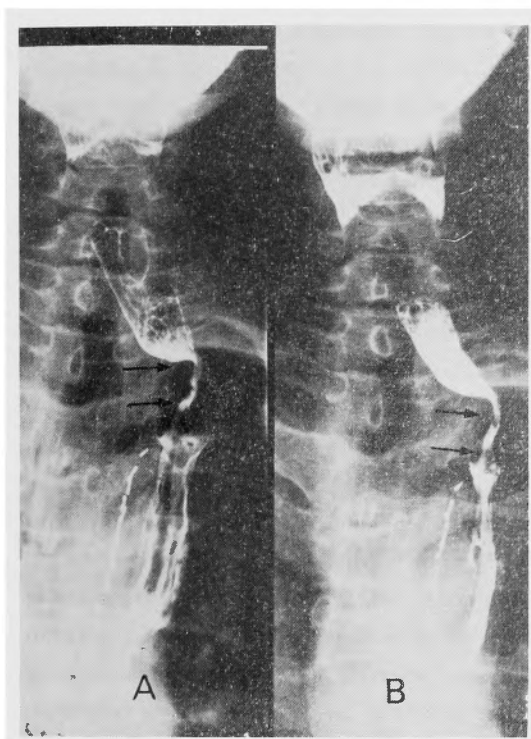


Fig. 15. Case 2. The esophagogram showed a stenotic lesion at the site of the antethoracic esophagogastrostomy (A). After treatment of intraluminal administration of BLM combined with iontophoresis, the esophagogram showed the improvement in swallowing (B).

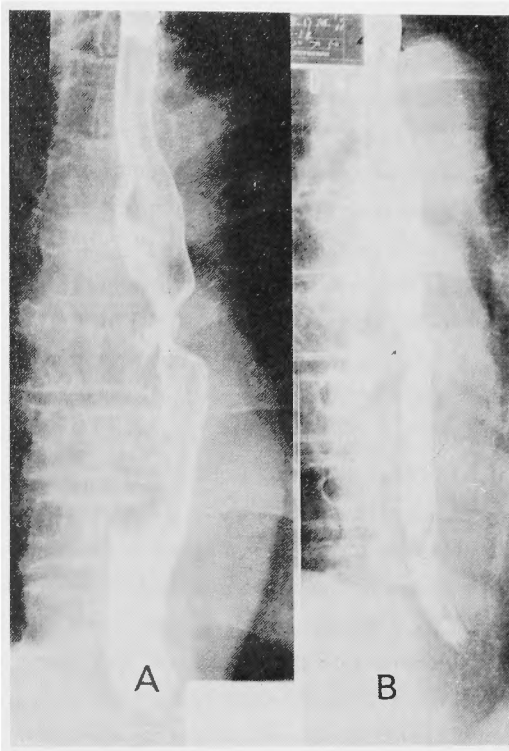


Fig. 16. Case 3. Before treatment, the esophagogram showed a long obstructive lesion in the lower two-thirds of the thoracic esophagus (A). After treatment of intraluminal administration of BLM combined with iontophoresis, the stenotic lesion became smooth (B).

combined with iontophoresis, he may show an improvement in swallowing and can take sufficient food to improve his general condition. As this method is not so effective on the main lesion of the esophagus as compared with radiotherapy, and the preoperative radiotherapy makes it possible to insert a double balloon catheter through a narrower segment of the affected esophagus, this method is used combined with radiotherapy when necessary.

Discussion

Local treatments for esophageal cancer comprise surgical operation, radiation therapy and local chemotherapy. In regards to preoperative radiation therapy, CLIFFTON reported that the rate of resectability of the esophageal cancer improved remarkably from 38% to 56% by this method⁷⁾. In 1967 NAKAYAMA reported that the rate of 5-year survival of esophageal cancer was ameliorated by preoperative radiation therapy²⁷⁾. AKAKURA reported that the rate of radical resectability of the esophageal cancer showed a marked improvement from 25.8% to 67.6% by radiation therapy¹⁾. As mentioned above the effectiveness of

preoperative radiation therapy on the esophageal cancer, especially in advanced cases, has been demonstrated by many authors¹⁸⁾¹⁹⁾³⁵⁾³⁹⁾⁵⁰⁾. Since then, for the purpose of prevention of side effects by radiation therapy, the administration of anticancer agents has been combined with radiation therapy. BLM, which was discovered by UMEZAWA in 1966, showed a selective effect on squamous cell carcinoma and malignant lymphomas³⁾¹⁴⁾¹⁵⁾¹⁷⁾²⁴⁾⁴¹⁾⁵²⁾⁵⁴⁾. Recently, the combined treatment of radiation and BLM has been used ordinarily as preoperative adjuvant chemotherapy⁴⁾⁵⁾⁸⁾²⁰⁾⁴⁸⁾⁵⁰⁾⁵⁶⁾⁵⁸⁾. BLM is an antitumor antibiotics isolated from *Streptomyces verticillus*, and is a water-soluble, basic glycopeptide. When BLM is injected into the rat, the drug distributes to the skin, the esophageal mucosa, the kidneys and the lungs in high concentrations, and is inactivated more slowly and remains for a long period in these tissues⁹⁾¹⁰⁾¹²⁾²³⁾⁴⁰⁾⁵¹⁾. According to UMEZAWA, BLM has been postulated to bind to DNA, causing a single strand scission in the presence of a sulfhydryl component, thereby inhibiting DNA synthesis and cell growth²⁵⁾⁴²⁾⁵³⁾. Main side effects of BLM administration are fever, anorexia and pulmonary complications, especially pulmonary fibrosis, which are most troublesome for the esophageal surgery, but hematopoietic disturbances are minimal⁴⁾⁶⁾¹⁶⁾. The drug has been administered in systemic and local therapy. Local administrations of BLM for esophageal cancer have been performed using various methods, that is, intramural injection into the esophageal wall using endoscopy, selective intraarterial infusion using Seldinger's procedure, continuous infusion into the posterior mediastinum, local administration using sponge-BLM during operation, solid BLM embedding into the abdominal cavity during operation and intraluminal administration²¹⁾²²⁾²⁶⁾²⁹⁾³⁰⁾⁴⁶⁾⁴⁷⁾⁵⁷⁾. When BLM solution was injected into the wall of the esophagus of the dog, the drug spread toward the oral and aboral portions of the esophagus, by way of the intramural lymphatics and reached the regional lymph nodes in great amounts and was absorbed into the blood for a short period. The drug did not remain in the injected portion for a long time. According to SHIBATA who studied on BLM concentration in the regional lymph nodes of the esophagus and the lungs following various administration sites, BLM levels in the esophagus and intrathoracic regional lymph nodes increased following local injection into the esophageal wall, intravenous injection and selective intraarterial infusion into the ascending branch of the left gastric artery, in the order mentioned, and the levels in the lungs were lowered following intravenous injection, selective intraarterial infusion and local injection, in the order mentioned. Therefore, local injection of BLM into the esophageal wall is of great importance and advantageous as a preoperative chemotherapy for cancer of the esophagus⁴⁰⁾. Because this method is troublesome and is a burden to the emaciated patients with esophageal cancer, it is difficult for the doctor to perform this treatment repeatedly. On the other hand, when BLM was administered into the lumen of the esophagus, using a double balloon catheter, the drug was absorbed only slightly into the esophageal wall. But when the defect of the mucosa happened in the esophagus of the dog, the drug was absorbed massively into the esophageal wall, lymph and blood and distributed to the regional lymph nodes. BLM concentration in the lungs in this method of administration was lower than that in the local injection into

the lumen of the esophagus. Therefore, BLM administration into the lumen of the esophagus using double balloon catheter is advantageous as a preoperative adjuvant chemotherapy for esophageal cancer. Moreover, this method is easy to put into practice and will unlikely induce pulmonary complications. The author presumes that BLM solution is absorbed abundantly from the surface of cancer of the esophagus and reaches to the regional lymph nodes following administration into the lumen using a double balloon catheter. Furthermore, based on the reports by HAYASHIZAKI, BLM-Iontophoresis was combined with this method¹³⁾. Then the drug permeated abundantly through the normal esophageal mucosa and reached to the regional lymph nodes. This method of treatment causes little trouble to the patients and produces few side effects, so we may perform this method of treatment repeatedly as a preoperative chemotherapy and may expect good effects on dysphagia and metastases to the regional lymph nodes. Most of the cases who received this treatment showed an improvement in swallowing and increased their food intake after 3 or 4 treatments. That is to say, this method of treatment is of great advantage to improve the general condition. But we cannot expect the anticancer effect on main lesion of the esophagus by this method as compared with radiation therapy. Therefore, radiation therapy may be needed to be combined with this treatment. This treatment is used not only in the preoperative adjuvant chemotherapy, but also for the stricture by recurrence at the esophagogastrostomic region, as seen in case 2. Side effects of this method of treatment are few. Recently, transient sore throat had been complained of after this treatment, but fever and pulmonary complications were not experienced until today. Intramural injection of BLM into the esophageal wall is more effective on metastatic lymph nodes. TAKAHASHI mentioned that the emulsion type of BLM was apt to ambulate into the regional lymph nodes and stay there for longer time⁴⁴⁾⁴⁵⁾. Local chemotherapy for metastatic lymph nodes has been performed by various methods, that is, infusion of BLM emulsion into the posterior mediastinum (by INOUCHI²¹⁾), and insertion of BLM-spongel (by NAKAMURA²⁶⁾) or solid-BLM (by WATANABE⁵⁷⁾). Recently, Oil-bleomycin has been used in local chemotherapy for cancer of the esophagus by local injection³⁶⁾. This type of BLM remains in the injected tissue for a long time, so it may be more effective than the solution type as local chemotherapy¹¹⁾.

Conclusion

For the purpose of improving the curability of esophageal cancer, the author studied on local chemotherapy of the esophageal cancer, especially BLM administration into the lumen of the esophagus combined with BLM-Iontophoresis and local injection of BLM into the wall of the esophagus. The results were as follows : 1) When BLM solution was injected into the wall of the esophagus, the drug was absorbed into the azygos vein blood and the thoracic duct lymph in great amounts for a short period and then spread toward the oral and aboral portions of the esophagus by way of the intramural lymphatics and reached the regional lymph nodes in high concentration. In the esophagus, BLM levels in

the injected portion showed high values 30 minutes after injections and was lowered rapidly for 2 hours. And BLM solution did not remain in the esophageal wall for a long period. 2) When BLM was administered into the lumen of the esophagus the drug was absorbed only slightly through the normal mucosa of the esophagus. When the mucosa of the esophagus was removed, the drug was absorbed sufficiently into the azygos vein blood and the thoracic duct lymph. BLM concentrations in the azygos vein blood and the thoracic duct lymph were approximately in proportion to the extent of the mucosal defect, that is, the wider the mucosal defect was, the higher and the sooner the peak level of BLM in the blood and the lymph appeared. 3) BLM was inactivated by the direct electric current. The drug was inactivated approximately in proportion to the intensity and the duration of the direct current. The inactivation occurred less in the solution whose pH ranged from 4 to 7. 4) Movement of BLM in the application of agar gel electrophoresis at 10 mA for 30 minutes was as far as 3 cm from the original site on the side of the cathode. 5) When BLM administration into the lumen of the esophagus was combined with iontophoresis, the drug permeated massively into the esophageal wall through the normal mucosa reaching to the regional lymph nodes. 6) Histochemical observation showed that BLM might permeate into the esophageal tissue through the normal mucosa from the lumen or via the ducts of esophageal glands in the opposite direction. 7) This method of treatment was performed on 14 clinical cases who had suffered from cancer of the esophagus. Of 14, six patients showed an improvement in swallowing after receiving this treatment 3 or 4 times. Side effects of this treatment were few. This method of treatment is advantageous as a preoperative adjuvant chemotherapy for the esophageal cancer, because patients may show the early improvement in swallowing by this treatment and may be able to take sufficient food intake. The author thinks that the adequate dosage of this treatment is 15 mg to 45 mg of BLM in the physiological saline solution and the adequate number of times is twice or three times a week.

From these results BLM administration into the lumen of the esophagus using double balloon catheter combined with iontophoresis is effective on the esophageal cancer as an adjuvant local chemotherapy. Furthermore, this treatment will be more effective in combination with radiation therapy.

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和文抄録

食道癌の手術合併局所化学療法に関する研究，
とくに Double Balloon Catheter および
電気泳動の応用

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食道癌の根治性を向上させるための局所化学療法として、BLM 食道壁内局注と食道内腔内 BLM 投与法について検討し、さらにこれを臨床例に応用して、相当の効果をを得ることができた。実験成績および臨床例の検討より次のような成績を得た。

- 1) BLM の壁内局注の場合に、BLM は奇静脈血および胸管リンパに迅速に吸収され、さらに壁内リンパ流によって食道の頭尾側によく広がり、所属リンパ節に高濃度に分布した。しかし食道の BLM 濃度は BLM 生食水溶液局注の場合には短時間後に低値となった。
- 2) BLM の食道内腔内投与法では正常粘膜よりの BLM の吸収はほとんど認められなかったが、粘膜に欠損があると、その大きさに比例して血中およびリンパ中の BLM 濃度は高値を示し、その頂値も早く出現した。さらに投与局所で BLM 濃度は高値に達し、また BLM は所属リンパ節にも分布した。
- 3) BLM は通電によって不活性化を受けたが、その程度は電流の強さと通電時間にほぼ比例した。この不活性化は BLM 溶媒の pH が 4~7 の場合が軽度であった。
- 4) BLM は電気泳動によって陰極側に移動した。
- 5) BLM-Iontophoresis によって BLM は切除食道内によく浸透した。Iontophoresis の場合には BLM

の溶媒として生食水溶液が不活性化と組織浸透性の面よりすぐれていた。

- 6) 食道内腔内 BLM 投与法に Iontophoresis を併用すると正常食道粘膜よりの BLM の浸透が促進され、さらに所属リンパ節にも BLM を検出した。
- 7) 含銅ブレンオを使用した組織化学的実験成績より判定すると、BLM の食道内腔よりの浸透は正常上皮を通過するか、または食道腺を逆行して浸透すると考えられた。
- 8) 食道内腔内 BLM 投与法に電気泳動を併用する場合には電流は 5 mA 以下、30分以内が安全であり、BLM の投与量は 15mg~45mg/20ml 生食水、週 2~3 回が適当と考えられる。
- 6) 食道内腔内 BLM 投与法の臨床例の検討：14例に施行し、6例に 3~4 回の施行で通過状態の改善と食事摂取量の増加を認めた。とくに放射線との併用の 4 例中 3 例は著効を呈した。副作用は軽度の咽頭痛のほか 2 例に少量の出血を認めた。以上の成績より、手術合併療法として BLM 内腔内投与法を行うと通過状態の改善が早期より得られ、全身状態の改善を期待でき、副作用も少い点より有用であり、放射線療法との併用によってさらに効果が大きくなることが明らかとなった。